Non-motor symptoms in Parkinson's disease

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Nighttime sleep problems and daytime sleepiness in Parkinson's disease

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Abstract

Our objective is to evaluate nighttime sleep problems (NSP) and daytime sleepiness (DS) in patients with Parkinson's disease (PD) compared to controls, and to assess relations with demographic, disease-related, and clinical characteristics in patients. NSP and DS were evaluated with the SCOPA-SLEEP questionnaire in PD patients and controls. In patients, other disease-related and clinical characteristics were also evaluated. Four hundred twenty PD patients (mean (SD) age 61.1 (11.5) years) and 150 controls (mean (SD) age 60.9 (9.9) years) participated in the study. Compared to controls, a significantly greater proportion of patients had excessive DS (EDS) (43% versus 10%), excessive NSP (ENSP) (27% versus 9%), or used sleep medication (17% versus 12%). Difficulties with falling asleep were similar in both groups. In both patients and controls, women experienced more NSP than men. In patients, depressive symptoms accounted for 21% of NSP variance and was the major contributor to the total explained variance (30%). Furthermore, NSP were related to dopamine-agonist and levodopa dose, whereas DS was related to age, dopamine-agonist dose and disease severity. NSP and DS occur frequently in PD, with EDS being reported more commonly than ENSP. No strong relations were found between DS and demographic or clinical variables. The strong relation between NSP and depressive symptoms in PD calls for future studies to explore the nature of this relation.

Introduction

In Parkinson's disease (PD), nighttime sleep problems (NSP) and daytime sleepiness (DS) are regarded important non-motor symptoms, which also include depression, cognitive impairment, olfactory disturbances and autonomic dysfunction.[1] In PD, NSP mainly concern problems with maintaining sleep, whereas difficulties with falling asleep generally are not different compared to elderly without PD.[2,3] DS, described as inappropriate and undesirable sleepiness during waking hours, may occur in elderly, but is much more frequent in PD patients.[4]

Both the disease process and anti-parkinsonian medication are usually considered causative factors of NSP and DS in PD.[5] However, reported prevalences of NSP (18%-98%) and DS (11%-84%) vary widely[6,7] and relations between NSP/DS and demographic, disease-related and clinical variables have yielded inconsistent findings.[3-5,8-11] Potential explanations for these inconsistencies include differences between studies concerning criteria for NSP/DS, study populations, and type and methodological quality of the applied assessment methods.[3]

NSP and DS are common in PD, and have a significant negative impact on the well-being of patients and their spouses.[5,9] Hence, recognition and better understanding of factors contributing to NSP and DS may have important consequences for patient management.[12] The first aim of this study was to evaluate the occurrence of NSP/DS with a reliable and valid questionnaire[13,14] in PD patients and to compare this with controls. The second aim of this study was to assess relations between NSP/DS and demographic, disease-related and clinical characteristics in patients.

Methods

Design

The study is part of the "PROfiling PARKinson's disease" (PROPARK) study, a longitudinal cohort study of PD patients, who are profiled on phenotype, genotype, disability, and global outcomes of health using valid and reliable assessment instruments for PD. Findings obtained from the first annual evaluation of 420 patients assessed between May 2003 and March 2006 were used for analysis.

Participants

All patients fulfilled the United Kingdom Parkinson's Disease Society Brain Bank criteria for idiopathic PD.[15] Patients were recruited from both university and regional hospitals in the western part of The Netherlands. Patients were stratified according to age at onset (AO; onset of the first symptoms as perceived by the patient ≤ / > 50 years) and disease duration (≤ / > 10 years), because these characteristics are important determinants of disease course in PD.[16] Inclusion of patients stopped when ~100 patients were included in each stratum. No other selection criteria were applied. The majority of patients were assessed at the Leiden University Medical Center (LUMC). To avoid bias towards recruiting less severely affected patients, patients who were unable to come to the hospital were assessed at home.

Controls were selected to match the overall age and sex distribution of the patients, and had no documented diseases of the CNS. Partners were not eligible as controls as NSP of patients may affect the quality of nighttime sleep of their partner. One-hundred controls were acquaintances of participating patients with sporadic PD and fifty other controls were employees working in our hospital. The study was approved by the medical ethical committee of the LUMC and all participants gave informed consent.

Measurement instruments

Within PROPARK, all patients received standardized assessments, including evaluation of demographic and clinical characteristics, family history of PD, and medication use. Measurement instruments for the different clinical domains of PD were derived from a prior project (SCales for Outcomes in PArkinson's disease: SCOPA).[17]

For the current study, data obtained for NSP and DS (SCOPA-SLEEP)[13], disease severity (Hoehn & Yahr (H&Y))[18], motor function (SPES/SCOPA-motor, range 0-42)[19], autonomic function (SCOPA-AUT, range 0-69)[20], depressive symptoms (Beck Depression Inventory (BDI), range 0-63)[21], cognition (SCOPA-COG, range 0-43)[22], dyskinesias and motor fluctuations (SPES/SCOPA-motor complications, range 0-6 for both subscales)[19], and psychiatric complications (modified-PPRS,

range 0-18)[23] were used. Except for the SCOPA-COG, higher scores indicate more severe impairment. Except for the BDI, all instruments were specifically developed for PD. Data of controls included SCOPA-SLEEP, demographic characteristics and medication use.

The SCOPA-SLEEP is a self-administered questionnaire consisting of two sections. The NSP section addresses nighttime sleep problems in the past month and consists of five items with four response options (0 (not at all) to 3 (a lot)), with a maximum score of 15. The DS section evaluates daytime sleepiness in the past month, and includes six items with four response options (0 (never) to 3 (often)), with a maximum score of 18. Additionally, one item assesses overall sleep quality with seven response options (0 (slept very well) to 6 (slept very badly)). To discriminate between patient groups according to their sleep problems, suggested cut-off points of the NSP (6/7) and DS (4/5) section were used[13], resulting in four patient groups: patients without sleep problems, patients with only excessive NSP (ENSP), patients with only excessive DS (EDS), and patients with both ENSP and EDS. The BDI[21] is a self-administered questionnaire assessing severity of depressive symptoms. In this study the adjusted cut-off score for PD patients of 14/15 was used to discriminate between depressed and non-depressed patients.[24]

All instruments were either self-administered (SCOPA-SLEEP, SCOPA-AUT, BDI) or administered by trained research associates (H&Y, SPES/SCOPA-motor, SCOPA-COG, SPES/SCOPA-motor complications, modified-PPRS). For reasons of comparability, all patients using levodopa or a dopamine-agonist and experiencing motor fluctuations, were assessed during "on"-state. For each patient, a levodopa equivalent (LDE) for the dose of levodopa (LDE-Dopa) and dopamine agonists (LDE-DA) was calculated, and a total LDE was calculated by adding up these equivalents.[25]

Statistical analysis

If 25% or more of the data from a questionnaire or scale was missing, data from that instrument for that patient was excluded from statistical analyses. Differences between patients and controls, men and women, patients with and without sleep

medication, and between groups with different sleep problems were analyzed with student's T-tests, Mann-Whitney-U tests, χ^2 tests, and analysis of variance. Pearson's correlation coefficients were used to assess relations between variables. In patients, multiple forward linear regression analysis was used to explore the contribution of different variables to NSP/DS total score, using separate blocks (blocks 1 to 3: demographic, disease-related, and clinical variables). A p-value < 0.05 was considered significant. All analyses were performed with Statistical Package for the Social Sciences 12.0.1 Software (SPSS 12.0.1).

Results

One patient had too many missing values on both SCOPA-SLEEP sections and was excluded from the study. Therefore, 419 patients (64% men) and 150 controls (55% men) participated in this study. Furthermore, one patient and one control were excluded from analyses for the DS section only, because of too many missing values. Patients had a mean (SD) age of 61.1 (11.5) years and a mean (SD) disease duration of 10.5 (6.5) years (Table 1).

Controls

In controls, no significant correlations between NSP and DS or between both sleep problems and age existed. Women experienced more NSP than men, with higher total section scores (mean scores 3.5 versus 2.3 (mean difference 1.1, 95% CI 0.3 to 2.0)) and item scores for "difficulty falling asleep" (p=0.008) and "been awake too often" (p=0.006). Women also reported worse overall sleep quality (p=0.007). There were no differences between men and women regarding DS.

PD patients versus controls

Patients had more NSP and DS compared to controls, with higher total section scores (NSP: mean scores 4.5 versus 2.9 (mean difference 1.7, 95% CI 1.1 to 2.2), DS: mean scores 4.9 versus 2.0 (mean difference 2.8, 95% CI 2.3 to 3.3)) and item

scores, except for the NSP item "difficulty falling asleep" (Table 2). Patients also had worse overall sleep quality (p<0.001). Relative to controls, more patients had ENSP (total NSP section score ≥7; 27% versus 9%, p<0.001), had EDS (total DS section score ≥5; 43% versus 10%, p<0.001), and used sleep medication (17% versus 12%, p=0.005).

Table 1. Characteristics of participants

Characteristics	Patients	Controls
No. of participants	419	150
Sex m/w (% men)	266/153 (64%)	82/68 (55%)
Age, mean (SD), years	61.1 (11.5)	60.9 (9.9)
Employed, no. (%)	104 (25%)	50 (33%)
Disease duration, mean (SD), years	10.5 (6.5)	-
Age at onset, mean (SD), years	50.6 (12.0)	-
Hoehn and Yahr stage, no. (%)		-
1	15 (4%)	
2	201 (48%)	
3	110 (26%)	
4	71 (17%)	
5	11 (3%)	
Missing	11 (3%)	
Total LDE, mean (SD), mg/day	608.0 (461.4)	-
LDE-Dopa, mean (SD), mg/day	378.1 (373.4)	-
LDE-DA, mean (SD), mg/day	230.2 (223.3)	-
Beck Depression Inventory, no. (%)		-
Depressed	88 (21%)	
Non-depressed	329 (79%)	
Missing	2 (0%)	

LDE: levodopa dosage equivalent; DA: dopamine-agonist

Table 2. Frequency of nighttime sleep problems and daytime sleepiness in controls and patients (% with an item score ≥1)

			Patients	Controls
	Item	**N**	419	150
NSP	1. Difficulty falling asleep		36	40
	2. Been awake too often		71[1]	61
	3. Lying awake too long		58[1]	47
	4. Waking too early		62[1]	43
	5. Had too little sleep		60[1]	44
DS	1. Falling asleep unexpectedly		67[1]	38
	2. Falling asleep while sitting		71[1]	42
	3. Falling asleep while watching TV		72[1]	51
	4. Falling asleep while talking		15[1]	0
	5. Difficulty staying awake		77[1]	46
	6. Falling asleep considered a problem		32[1]	8

[1]: significant difference (p<0.05) with controls (Mann-Whitney-U test)

Determinants of NSP and DS in patients

In patients, women had more NSP than men with higher total section scores (mean scores 5.1 versus 4.2 (mean difference 0.9, 95% CI 0.1 to 1.6)) and item scores for "difficulty falling asleep" (p=0.044) and "waking too early" (p=0.009). Women also reported worse overall sleep quality (p=0.033). There were no differences between men and women regarding DS. NSP and DS scores correlated weakly (r=0.2, p<0.001). Female gender, higher LDE-DA, higher LDE-Dopa, more depressive symptoms, better cognition and more motor fluctuations together accounted for 30% of NSP variance (p<0.001), with depressive symptoms as major contributor (21%;Table 3). To gain further insight in the role of depressive symptoms in NSP, the regression analysis was performed separately for non-depressive (n=329) and depressive patients (n=88). In non-depressive patients, younger age, higher LDE-DA, higher LDE-Dopa, more depressive symptoms, more motor fluctuations and better cognition together accounted for 24% of NSP variance (p<0.001), with depressive symptoms

still as major contributor (11%). Thus, although these patients had BDI scores below the cut-off value and therefore did not fulfill the criteria for depression in PD, they did experience some depressive symptoms that contributed to NSP. In depressive patients, depressive symptoms were the only contributor to NSP accounting for 8% of the variance (p=0.017).

In DS, higher age, lower AO, higher LDE-DA, more severe PD, more autonomic problems, less dyskinesias and more psychiatric problems together accounted for 24% of the variance (p<0.001; Table 3). All variables only made a small contribution.

Table 3. Regression analysis of NSP and DS sections of the SCOPA-SLEEP in patients with PD

SCOPA-SLEEP section	Variable[1]	R square
NSP[2]	Sex	0.01
	LDE-DA	0.03
	LDE-Dopa	0.02
	Depressive symptoms	0.21
	Cognitive functioning	0.02
	Motor fluctuations	0.01
	Total	0.30
DS[2]	Age	0.03
	Age at onset	0.06
	LDE-DA	0.03
	Disease severity	0.02
	Autonomic functioning	0.04
	Dyskinesias	0.04
	Psychiatric complications	0.02
	Total	0.24

[1]: variables are ordered in the table as they appeared in the model

[2]: multiple forward linear regression analysis was used with variables forced in three blocks: block 1 (demographic): age and sex; block 2 (disease-related): age at onset, LDE-Dopa, LDE-DA, and disease severity; block 3 (clinical): cognitive functioning, autonomic functioning, depressive symptoms, dyskinesias, motor fluctuations, and psychiatric complications

NSP: nighttime sleep problems; DS: daytime sleepiness; LDE: levodopa dosage equivalent; DA: dopamine-agonist

Table 4. Characteristics of subgroups of patients with different types of sleep problems

Characteristics	No sleep problems
No. of patients	187
Sex m/w (% men)	126/61 (67%)
Age, mean (SD), years	59.8 (11.8)[1]
Disease duration, mean (SD), years	8.8 (5.9)
Age at onset, mean (SD), years	51.0 (12.5)
Hoehn and Yahr stage, no. (%)	
1	9 (5%)
2	108 (58%)
3	47 (25%)
4	16 (9%)
5	3 (2%)
Missing	4 (2%)
Total LDE, mean (SD), mg/day	474.1 (462.2)
LDE-Dopa, mean (SD), mg/day	295.4 (371.2)
LDE-DA, mean (SD), mg/day	178.7 (220.2)
Use of medication for nighttime sleep problems, no. (%)	18 (10%)[4,5]
SCOPA-AUT score, mean (SD)	14.2 (7.4)
SCOPA-COG score, mean (SD)	27.2 (5.6)[1]
SPES/SCOPA-motor score, mean (SD)	12.2 (4.4)[1,6]
Dyskinesia score, mean (SD)	0.7 (1.4)
Motor fluctuations score, mean (SD)	0.5 (1.1)
Modified-PPRS score, mean (SD)	1.5 (1.5)[6]
BDI score, mean (SD)	7.4 (4.9)

[1]: significant difference ($p<0.05$) with the patient group with only EDS (ANOVA)

[2]: significant difference ($p<0.05$) with the patient group without sleep problems (ANOVA)

[3]: significant difference ($p<0.05$) with the patient group without sleep problems (χ^2 test)

[4]: significant difference ($p<0.05$) with the patient group with only ENSP (χ^2 test)

[5]: significant difference ($p<0.05$) with the patient group with both ENSP and EDS (χ^2 test)

[6]: significant difference ($p<0.05$) with the patient group with both ENSP and EDS (ANOVA)

Only ENSP	Only EDS	Both ENSP and EDS
51	118	62
24/27 (47%)	77/41 (65%)	39/23 (63%)
58.2 (11.5)[1]	64.5 (10.1)	61.2 (11.9)
11.3 (5.9)	12.2 (7.2)[2]	11.8 (6.6)[2]
46.8 (10.6)[1]	52.3 (11.1)	49.4 (12.4)
	[3]	[3]
3 (6%)	1 (1%)	2 (3%)
24 (47%)	47 (40%)	22 (35%)
13 (25%)	28 (24%)	22 (35%)
9 (18%)	32 (27%)	13 (21%)
1 (2%)	5 (4%)	2 (3%)
1 (2%)	5 (4%)	1 (2%)
694.6 (465.0)[2]	695.6 (433.8)[2]	760.5 (395.1)[2]
437.3 (369.5)	427.5 (368.7)[2]	472.8 (337.2)[2]
259.6 (220.1)	268.1 (213.6)[2]	287.7 (226.9)[2]
17 (33%)	12 (10%)[4,5]	24 (39%)
18.9 (8.0)[2,6]	20.0 (7.7)[2,6]	24.3 (8.2)[2]
26.6 (6.3)[1]	23.4 (6.4)	25.3 (6.2)
13.2 (4.9)[1]	15.3 (5.3)	14.8 (4.8)
1.5 (2.0)[2]	0.9 (1.6)	1.1 (1.6)
1.6 (1.6)[1,2]	0.6 (1.1)	1.1 (1.4)[1,2]
2.0 (1.7)[6]	2.6 (2.2)[2,6]	3.5 (2.2)
13.3 (7.2)[1,2]	10.5 (5.5)[1,2]	16.1 (7.9)[1,2]

ENSP: excessive nighttime sleep problems; EDS: excessive daytime sleepiness;
LDE: Levodopa dosage equivalent; DA: dopamine-agonist; modified-PPRS: modified-Parkinson Psychosis Rating Scale; BDI: Beck Depression Inventory

Sleep medication in patients

Seventy-two patients (17%) used sleep medication in the past month. These patients had more NSP with higher total section scores (mean scores 7.3 versus 4.0 (mean difference 3.3, 95% CI 2.2 to 4.3)), but no more DS (mean scores 5.6 versus 4.7 (mean difference 0.8, 95% CI -0.2 to 1.8)) compared to patients without sleep medication. Furthermore, patients using sleep medication were older (mean difference 4.3, 95% CI 1.6 to 6.9), included more women (p=0.037), and had higher LDE (mean difference 127.0, 95% CI 10.1 to 243.8). Additionally, they had more severe PD (p<0.001), more motor impairment (mean difference 1.7, 95% CI 0.4 to 3.0), autonomic problems (mean difference 4.9, 95% CI 2.8 to 7.0), and depressive symptoms (mean difference 4.8, 95% CI 2.6 to 7.0).

Subgroup analysis of patients with different types of sleep problems

Patients were classified according to presence or absence of sleep problems (patients without sleep problems (n=187), patients with only ENSP (n=51), patients with only EDS (n=118), and patients with both ENSP and EDS (n=62)).

Patients with only EDS were the oldest, with the highest AO, longest disease duration, and most severe PD. Patients with both ENSP and EDS had the highest treatment doses (total LDE, LDE-Dopa and LDE-DA). Patients without sleep problems had the least problems on other impairment domains, including motor, autonomic, and cognitive functioning, motor and psychiatric complications, and depressive symptoms. Patients with only EDS had significantly more motor and cognitive impairment compared to patients with only ENSP, whereas patients with only ENSP experienced significantly more depressive symptoms and motor fluctuations (Table 4).

Discussion

In this study, relatively more PD patients than age- and sex-matched controls experienced ENSP (27% versus 9%) and EDS (43% versus 10%). In line with others, women experienced more NSP compared to men in both patients and controls.[11,26] For falling asleep, no differences were found between both groups, which was reported previously.[2,3] Apparently, some NSP are influenced by sex only (falling asleep), whereas others are influenced by both sex and disease (maintaining sleep).[27] We did not find the well known age-related influence on NSP in controls.[26] Because age-related NSP especially occur >75 years[26], this is most likely explained by our relatively young controls (mean age 61 years).

In this study, a forward regression model was used in which interrelations of factors in the model are taken into account. This model showed that NSP in patients were related to both LDE-DA and LDE-Dopa but not to disease severity, whereas DS was related to both LDE-DA and disease severity, but not to LDE-Dopa. From these relations, only the influence of LDE-DA on DS was consistently described by others.[8,11,28-30] Inconsistencies between our results and those of others could be explained by differences in criteria for the existence of NSP/DS, study populations, and type and methodological quality of applied assessment methods. For instance, the prevalence of ENSP found in our study was relatively low compared to others. This could be explained by our relatively young cohort (mean age 61 years), because other studies had older patient groups (mean ages 67-73 years).[2,6,27,31] Furthermore, the Pittsburgh Sleep Quality Index used in some studies includes items evaluating occurrence of NSP, daytime dysfunction, and use of sleep medication. Subsequently, all items are summed to a total score, making a comparison with the SCOPA-SLEEP, which evaluates only the occurrence of NSP, inappropriate.[9,11] Finally, differences in NSP prevalence between studies can also be explained by the use of different criteria for the existence of NSP.[10]

Depressive symptoms are highly prevalent in PD and related to both disease severity and NSP.[6,32] After controlling for disease severity influence, our study showed that depressive symptoms were the major contributor to NSP in PD. Several other studies,

with some controlling for the influence of disease severity, also found a relation between depression and NSP.[11,27,31,33] Patients who did not fulfill the criteria for depression in PD (BDI score ≤14), can still experience some depressive symptoms. Interestingly, we found that even in these patients, depressive symptoms remained the most important contributor to NSP, underscoring the importance of this relation. The direction of this relation is unknown due to the cross-sectional design of this study, but literature offers two views. In both patients and adults without PD, depression as a cause of NSP is most commonly described.[34,35] However, NSP preceding depression is reported by some in healthy elderly and therefore NSP may be regarded a risk factor for depression.[36,37] Because both depressive symptoms and NSP are important contributors of quality of life in PD[6], this relation needs further exploration. If PD patients with insomnia have an increased risk for developing depression, future studies may address if adequate management of NSP may prevent depression.

In addition to the association between depression and NSP, a few other relations were found between NSP/DS and other PD domains. More severe NSP was also related to better cognition and more motor fluctuations, whereas DS was related to more autonomic problems, less dyskinesias, and more psychiatric problems. None of these relations, except for relations between sleep quality and on-off phenomena[38], and DS and hallucinations[39], were described or evaluated by others.

In line with other studies, significantly more patients than controls used sleep medication.[8,27] Hypnotic and sedative agents, as well as antidepressants, may provide benefit in reducing NSP in PD.[8] However, based on NSP cut-off scores, in more than half of the patients using sleep medication the relief of NSP was still insufficient, which highlights the need for more efficacious therapies for NSP. Conversely, 40% of the patients using sleep medication had scores below the NSP cut-off, which may have led to an underestimation of NSP in this study.

Because of increased CNS sensitivity, elderly people generally are more sensitive to hypnotic drugs, especially benzodiazepines, which therefore may be a major contributor to DS, even after relatively short-term use.[26] We could not confirm this effect of sleep medication, which is possibly explained by the more prominent role

of other factors including dopaminergic medication in PD.

Patients with only EDS experienced more motor and cognitive problems compared to patients with only ENSP, whereas patients with only ENSP experienced more depressive symptoms and motor fluctuations. Although these differences may partly be explained by differences in age and AO between both groups, they may also suggest differential mechanisms underlying NSP and DS in PD. This is also supported by the weak correlation between NSP and DS.

Subjective assessment of sleepiness is limited by accuracy of self-reporting[27] and perception of sleepiness.[40] Additionally, chronic disease status and cognitive impairment may also influence perception and detection of sleep problems.[40,41] These disadvantages may have distorted the frequency of NSP and DS in patients in this study.[42] However, the aim of this study was to identify the frequency and severity of NSP and DS in a large sample of participants, in which a questionnaire is more useful.[27]

In summary, this clinic-based study shows that NSP and DS occur frequently in PD, with EDS being more common than ENSP. No strong relations were found between DS and demographic or clinical variables. The strong relation between NSP and depressive symptoms in PD calls for future studies to explore the nature of this relation. In this study, possible causes for sleep problems, such as nocturia or pain, were not evaluated. However, for patient management more insight in causes of sleep problems is important and therefore, further research with validated questionnaires considering these topics is necessary. Conclusions about the direction of relations found in this study cannot be drawn due to the cross-sectional design. Therefore, future prospective longitudinal research should focus on onset and development of NSP/DS and temporal relations with other variables to obtain better understanding of underlying mechanisms.

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